Genetic Diseases of Junctions

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Tight junctions, gap junctions, adherens junctions, and desmosomes represent intricate structural intercellular channels and bridges that are present in several tissues, including epidermis. Clues to the important function of these units in epithelial cell biology have been gleaned from a variety of studies including naturally occurring and engineered mutations, animal models and other *in vitro* experiments. In this review, we focus on mutations that have been detected in human diseases. These observations provide intriguing insight into the biological complexities of cell–cell contact and intercellular communication as well as demonstrating the spectrum of inherited human diseases that are associated with mutations in genes encoding the component proteins. Over the last decade or so, human gene mutations have been reported in four tight junction proteins (claudin 1, 14, 16, and zona occludens 2), nine gap junction proteins (connexin 26, 30, 30.3, 31, 32, 40, 43, 46, and 50), one adherens junction protein (P-cadherin) and eight components of desmosomes (plakophilin (PKP) 1 and 2, desmoplakin, plakoglobin – which is also present in adherens junctions, desmoglein (DSG) 1, 2, 4, and corneodesmosin). These discoveries have often highlighted novel or unusual phenotypes, including abnormal skin barrier function, alterations in epidermal differentiation, and developmental anomalies of various ectodermal appendages, especially hair, as well as a range of extracutaneous pathologies. However, this review focuses mainly on inherited disorders of junctions that have an abnormal skin phenotype.

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Introduction

To maintain the structure and function of the epidermis a number of intercellular junctions exist, including tight junctions, gap junctions, adherens junctions, and desmosomes. These cell–cell contacts have multiple and diverse roles in regulating aspects of tissue adhesion, signaling, communication, differentiation, migration, proliferation, shape, permeability, polarity, and development. Each junction is made up of complex networks of proteins, the precise composition of which may vary in a site-specific and differentiation-specific manner. In recent years, a number of naturally occurring human mutations have been detected in genes that encode several proteins that make up these junctions. In this review, we highlight the naturally occurring human mutations that constitute the ''genetic disorders of junctions''. Mutations in components

Editor's Note

The JID Perspectives Series on keratinocyte adhesion and cell junctions continues with a review of the mutations that occur in important proteins that make up the intercellular junctions of keratinocytes. In this issue, Lai-Cheong and coworkers provide a comprehensive review of human genetic diseases that have been found to arise from mutations of intercellular junction proteins. This review highlights the important collaborations that have developed in investigative dermatology among cell biologists, geneticists, and clinicians. This Perspective provides direct evidence of how the close interactions of these scientific teams – working both from bench to bedside and from bedside to bench – have led to the discovery of new molecules important in keratinocyte adhesion, an increased understanding of the mechanisms of many genetic diseases, and new approaches for the treatment of some of the most severe inherited diseases of the skin.

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Abbreviations: ARVC, arrhythmogenic ventricular cardiomyopathy; BPS, Bart–Pumphrey syndrome; CDSN, corneodesmosin; DSG, desmoglein; DSP, desmoplakin; KID, keratitis–ichthyosis–deafness; PKP, plakophilin; SPPK, striate palmoplantar keratoderma; ZO, zona occludens

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of tight junctions, gap junctions, adherens junctions, and desmosomes are described, although some mutated proteins, such as plakoglobin, are integral to both adherens junctions and desmosomes.

Tight junctions

Tight junctions have important roles in regulating epidermal barrier permeability by regulating the paracellular flux of water-soluble molecules between adjacent cells. The principal structural protein of tight junctions are the claudins, of which there are approximately 24 subtypes. Each of the claudins shows a unique tissue expression pattern with the main claudins in epidermis being claudin 1 and 4 (Furuse and Tsukita, 2006). Claudins also bind to other membrane macromolecules, including the zona occludens (ZO) proteins ZO-1, ZO-2, ZO-3, and multi-PDZ domain protein-1. Mutations in human claudin genes were first identified in 1999. Simon *et al.* (1999) reported one nonsense and a number of missense mutations in claudin 16 (also known as paracellin-1) in subjects with a rare autosomal-recessive renal disorder, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM248250); several other mutations in the claudin 16 gene, *CLDN16*, in this condition have subsequently been reported (Weber *et al.*, 2001), but no skin abnormalities have been noted in any affected individual. Apart from the kidney, tight junctions have key roles in other organs, including the ear and liver. Mutations in the claudin 14 gene, *CLDN14*, have been shown to underlie the autosomal-recessive deafness disorder DFNB29 leading to cochlear hair cell degeneration (Wilcox *et al.*, 2001). Mutations in the gene encoding the ZO-2 protein (also known as tight junction protein 2) have been reported as the basis for some cases of familial hypercholanemia, emphasizing the role of tight junctions in bile duct physiology (Carlton *et al.*, 2003). A rare X-linked neurodevelopmental disorder with congenital cataracts, Nance–Horan syndrome (OMIM302350), results from mutations in the gene encoding the Nance–Horan syndrome protein (Burdon *et al.*, 2003) which colocalizes with ZO-1 in tight junctions (Sharma *et al.*, 2006). However, dermatologic manifestations of inherited tight junction mutations are limited to genetic disorders of claudin 1.

Claudin-1

In 2002, Baala *et al.* (2002) mapped an unusual syndromic form of ichthyosis in consanguineous Moroccan families to a locus on chromosome 3q27–28. The cutaneous features comprised diffuse ichthyosis with large scales, *hypotrichosis, and scarring alopecia* as well as hypodontia. Other clinical abnormalities included sclerosing cholangitis and the disorder was termed neonatal ichthyosis and sclerosing cholangitis (OMIM607626). Vacuoles were noted in the affected individuals' eosinophils (and to a lesser extent basal keratinocytes). In addition, ultrastructural abnormalities were observed in the granular layer of the epidermis with disruption of intercellular connections, although widening of desmosomal plaques was the most prominent finding (Baala *et al.*, 2002). Given that the region of linkage in these families contained the claudin 1 gene, *CLDN1*, and that there were clear similarities between the human disease and the phenotype of mice deficient in claudin 1 (Furuse *et al.*, 2002), claudin 1 was a prime candidate for this disease and the first naturally occurring tight junction gene mutations with a skin phenotype were reported in 2004 (Hadj-Rabia *et al.*, 2004). Affected individuals were found to have a homozygous 2-bp deletion (*201_202del*) in exon 1 of *CLDN1* leading to complete loss of expression of this tight junction protein (Hadj-Rabia *et al.*, 2004). This mutation demonstrates the very important role of claudin 1 in human skin and liver biology.

Gap junctions

The first inherited abnormality of a gap junction protein was reported in 1993 with mutations in connexin 32 (encoded by the *GJB1* gene) in individuals with X-linked Charcot–Marie–Tooth disease (OMIM302800) (Bergoffen *et al.*, 1993). Then in 1997, mutations in the *GJB2* gene (encoding connexin 26) were identified in cases of congenital sensorineural deafness (DFNA3, OMIM601544; DFNB1, OMIM220290) (Kelsell *et al.*, 1997), a finding that led to the significant discovery that mutations in *GJB2* are in fact a common cause of several forms of congenital deafness. Subsequently, mutations have been discovered in seven other connexin genes: *GJB3* (connexin 31), *GJB4* (connexin 30.3), *GJB6* (connexin 30), *GJA1* (connexin 43), *GJA3* (connexin 46), *GJA8* (connexin 50), and most recently, *GJA5* (connexin 40) (Figure 1). Of these, four connexins are associated with skin diseases: connexins 26, 30, 30.3, and 31, although mutations in connexin 43 can also result in hair (and occasionally skin) abnormalities. Mutations in connexins 46 and 50 have been shown to underlie cases of zonular pulverent cataract, types CZP3 (OMIM601885) and CZP1 (OMIM116200), respectively (Berry *et al.*, 1999; MacKay *et al.*, 1999). Connexin 40 mutations have been implicated in some cases of idiopathic atrial fibrillation with somatic mutations in cardiac tissue or as a germline mutation (Gollob *et al.*, 2006).

Connexin 26

Mutations in *GJB2,* which encodes Cx26, can result in several distinct skin disorders including Vohwinkel's syndrome, keratitis–ichthyosis–deafness (KID) syndrome, Bart–Pumphrey syndrome (BPS), and syndromic sensorineural *hearing* loss with keratoderma (Figure 2a). The clinical abnormalities resulting from Cx26 mutations vary considerably but often involve skin hyperkeratosis (particularly palmoplantar keratoderma) and/or sensorineural deafness, usually with autosomal-dominant inheritance. The first connexin 26 mutation in a skin disease was described in a case of palmoplantar keratoderma with deafness (Richard *et al.*, 1998b). The genetic abnormality was a heterozygous missense mutation, p.R75W, which occurs within the second transmembranous domain. *In vitro* transfection studies showed this to be a dominant-negative mutation that disrupts normal connexon and gap junction function (Richard *et al.*, 1998b). Subsequently, three other missense mutations (p.G59A, p.G59R, and

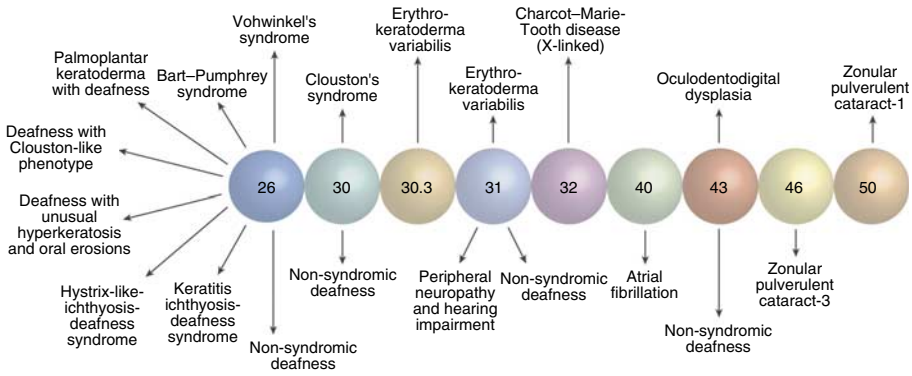

Figure 1. Illustration of disease phenotypes associated with abnormal gap junctions owing to inherited mutations in connexins. Most connexin disorders are autosomal dominant, although mutations in connexins 26, 31, and 43 can be associated with autosomal-recessive forms of deafness. In addition, recessive mutations in connexin 31 may underlie rare, recessive cases of EKV, and inheritance of connexin 32 mutations in Charcot–Marie–Tooth disease is X-linked.

p.R75Q) have been reported with this phenotype (Heathcote *et al.*, 2000; Uyguner *et al.*, 2002; Leonard *et al.*, 2005). Of note, the p.G59R case also had knuckle pads, suggesting phenotypic similarity to BPS (see below) (Leonard *et al.*, 2005). The second report of a connexin 26 mutation in a genodermatosis was made by Maestrini *et al.* (1999) in a case of Vohwinkel's syndrome (OMIM124500). Vohwinkel's syndrome is an autosomal-dominant disorder comprising palmoplantar keratoderma and pseudoainhum leading to autoamputation of digits, as well as varying degrees of sensorineural deafness. A heterozygous missense mutation, p.D66H, was identified in a large British pedigree containing 10 affected members. This connexin 26 mutation involves a residue within the first extracellular domain and is predicted to disrupt the assembly of connexin 26 into connexons as well as the docking and gating properties of the resulting gap junction. In 2002, a further connexin 26 genodermatosis was identified with the discovery of heterozygous missense mutations (p.G12R, p.S17F, and p.D50N) in KID syndrome (OMIM148210) (Richard *et al.*, 2002). KID syndrome is characterized by the triad of keratitis, hyperkeratotic plaques (mainly on the scalp and extremities, particularly palms and soles), and profound bilateral sensorineural hearing loss. The p.D50N mutation occurs within the highly conserved extracellular loop of connexin 26, an area critical for voltage gating (Rubin *et al.*, 1992), whereas the other two mutations (p.G12R and p.S17F) affect the cytoplasmic amino terminus and may disrupt the regulation of connexin selectivity and gating polarity (Verselis *et al.*, 1994; Falk *et al.*, 1997; Purnick *et al.*, 2000). The p.D50N mutation has also been reported subsequently in a case of hystrix-like-ichthyosis-deafness syndrome (OMIM602540), which clinically resembles KID syndrome (van Geel *et al.*, 2002). In addition, four other heterozygous mutations in the *GJB2* gene (p.N14Y, p.A40V, p.G45E, and p.D50Y) have been reported in other cases of KID syndrome (Yotsumoto *et al.*, 2003; Montgomery *et al.*, 2004; Janecke *et al.*, 2005; Arita *et al.*, 2006). Additional clinical features of a severe follicular occlusion triad were reported in two of these KID syndrome cases (p.A40V and p.D50N) (Montgomery *et al.*, 2004; Maintz *et al.*, 2005). In 2004, BPS (OMIM149200) was added to the spectrum of connexin 26 mutation-related disorders (Richard *et al.*, 2004). BPS (BPS) is an autosomal-dominant condition characterized by the combination of palmoplantar keratoderma, sensorineural deafness, knuckle pads, and leukonychia (Bart and Pumphrey, 1967). Richard *et al.* (2004) identified a heterozygous missense mutation, p.N54K, within the first extracellular domain. Subsequently, the mutation p.G59S was reported in another case of BPS (Alexandrino *et al.*, 2005). Mutations affecting p.G59 have also been reported in two cases of palmoplantar keratoderma with deafness (Heathcote *et al.*, 2000; Leonard *et al.*, 2005), suggesting clinical heterogeneity resulting from mutations in this residue of connexin 26. Expanding the clinical spectrum of connexin 26 disorders even further, the mutation p.N14K has been reported in a case of a Clouston's syndrome-like disorder associated with deafness (van Steensel *et al.*, 2004), although a mutation in this amino acid has also been described in KID syndrome (Arita *et al.*, 2006). In addition, the mutation p.F142L, which occurs within the third transmembranous domain of connexin 26, has been documented in a case of deafness associated with unusual mucocutaneous findings, including a psoriasiform dermatitis, oral erosions, and ear infections (Brown *et al.*, 2003). Clearly mutations in the *GJB2* gene are associated with protean clinical abnormalities. Moreover, genotype–phenotype correlation is difficult. For example, although in most cases of KID syndrome the connexin 26 pathology is close to the amino terminus, some cases of nonsyndromic deafness also involve similar mutations, for example, p.W44C (Denoyelle *et al.*, 1998). Moreover, particular mutations can be associated with different clinical phenotypes, as seen for the p.D50N and p.G45E mutations. Of note, p.G45E has been reported in KID syndrome patients (Janecke *et al.*, 2005), but this is also one of the most common mutations in nonsyndromic

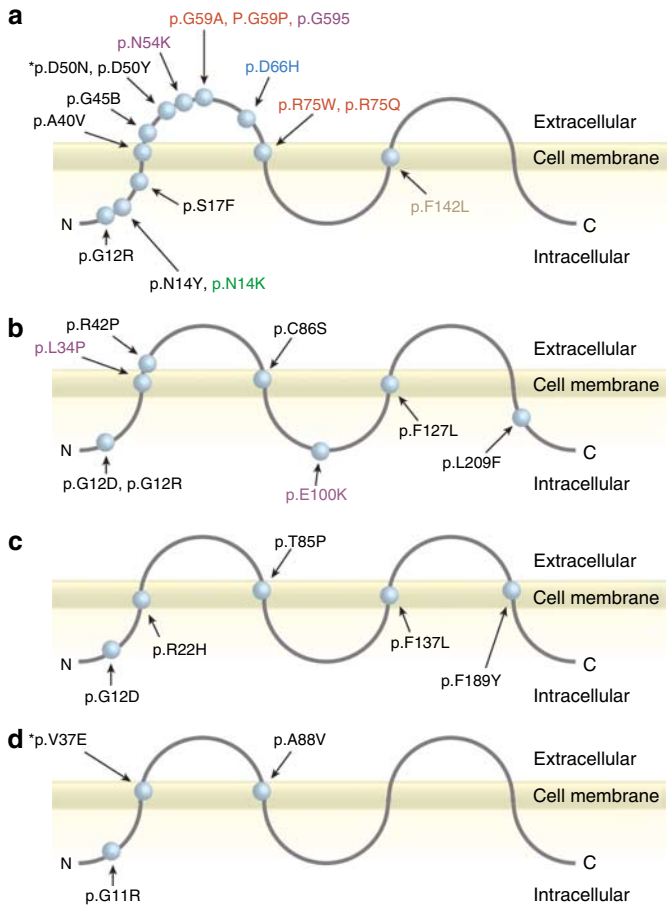

Figure 2. Mutation spectrum and skin disease phenotypes for the gap junction proteins connexin 26, 30, 30.3, and 31. Mutations associated with hearing loss/impairment in the absence of skin abnormalities are not shown (**a**) Mutations in connexin 26: 16 different mutations have been associated with various clinical abnormalities, including KID syndrome (black), palmoplantar keratoderma with deafness (red), Vohwinkel's syndrome (blue), BPS (purple), Clouston's syndrome-like disorder with deafness (green), and deafness with hyperkeratosis, oral erosions and other unusual mucocutaneous abnormalities (brown). Asterisk indicates a hystrix-like ichthyosis-deafness disorder has been reported with this mutation. (**b**) Mutations in connexin 31: eight different missense mutations have been identified in connexin 31. The majority have been associated with autosomal-dominant EKV, although the purple text indicates that a recessive form of EKV has been associated with these homozygous amino-acid substitutions. (**c**) Mutations in connexin 30.3: five different missense mutations have been described in connexin 30.3, all of which have been associated with autosomal-dominant EKV. (**d**) Mutations in connexin 30: three different missense mutations have been reported in connexin 30, two of which were in Clouston's syndrome (hidrotic ectodermal dysplasia) and one was associated with KID syndrome with congenital atrichia (indicated by asterisk).

autosomal-recessive deafness in Japanese individuals (Ohtsuka *et al.*, 2003).

Connexin 31

The first connexin 31 mutation (*GJB3* gene) was reported in a case of erythrokeratoderma variabilis (EKV; OMIM133200) (Richard *et al.*, 1998a) (Figure 2b). EKV characterized by transient figurate erythema and localized or generalized hyperkeratosis that develops soon after birth. EKV is usually an autosomal-dominant disorder, although recessive cases have also been reported (Gottfried *et al.*, 2002; Terrinoni *et al.*, 2004). In the report by Richard *et al.* (1998a) three heterozygous missense mutations, p.G12R, p.G12D, and p.C86S, were detected in four autosomal-dominant families with EKV (Richard *et al.*, 1998a); additional amino-acid substitutions in connexin 31, p.R42P, p.F137L, and p.L209F, have also been reported in other EKV subjects (Richard *et al.*, 2000; Morley *et al.*, 2005). In 2002, Gottfried *et al.* (2002) reported the first autosomal-recessive EKV mutation with a homozygous mutation p.L34P which resulted in defective trafficking of connexin 31. An additional case of recessive EKV associated with the missense mutation p.E100K has also been reported (Terrinoni *et al.*, 2004). Although none of the reported EKV cases (dominant or recessive) has hearing impairment, mutations in connexin 31 have also been reported in familial cases of autosomal-dominant hearing impairment as well as autosomal-recessive hearing loss and peripheral neuropathy associated with hearing impairment (Xia *et al.*, 1998; Rabionet *et al.*, 2000; Lopez-Bigas *et al.*, 2001).

Connexin 30.3

Adding to the genetic heterogeneity of EKV, mutations in the *GJB4* gene, encoding connexin 30.3, were reported in 2000 (Macari *et al.*, 2000) (Figure 2c). These authors documented a heterozygous missense mutation, p.F137L, and other amino-acid substitutions in individuals with EKV, p.G12D, p.R22H, p.T85P, and p.F189Y, were also reported (Richard *et al.*, 2003). Of note, identical mutations (p.F137L and p.G12D) have been reported in connexin 31 in individuals with the same EKV phenotype. This observation suggests both a specific genotype–phenotype correlation between these mutations and EKV, but also a very similar function for connexins 30.3 and 31 in skin biology (Richard *et al.*, 1998a, 2000).

Connexin 30

Although a pathogenic mutation in the *GJB6* gene had been found in cases of autosomal-dominant nonsyndromic sensorineural deafness in 1999 (Grifa *et al.*, 1999), an association with inherited skin disease was not documented until the following year. Lamartine *et al.* (2000) reported the first examples of connexin 30 mutations in individuals with hidrotic ectodermal dysplasia (Clouston syndrome; OMIM129500) (Figure 2d). Clouston syndrome is an autosomal-dominant form of ectodermal dysplasia characterized by nail dystrophy, palmoplantar

hyperkeratosis, and alopecia with normal sweat gland function; some cases also have sensorineural hearing loss (Fraser and Der, 2001). The initial connexin 30 mutations reported by Lamartine *et al.* (2000) were p.G11R and p.A88V, and a further mutation, p.V37E, in a Scottish case of Clouston syndrome has also been documented (Smith *et al.*, 2002). Subsequently, the missense mutations p.G11R and p.A88V were identified in several patients with a clinical diagnosis of pachyonychia congenita (but lacking keratin gene pathology) (van Steensel *et al.*, 2003). Moreover, the mutation p.V37E has also been reported in a case of KID syndrome with congenital atrichia (Jan *et al.*, 2004). Thus, mutations in connexin 30 are associated with a spectrum of phenotypic abnormalities, although much of this may reflect differences in descriptive terminology used by different authors rather than separate disease entities.

Connexin 43

Mutations in the *GJA1* gene, encoding connexin 43, were first reported in 2001 in nonsyndromic deafness (Liu *et al.*, 2001) and for a syndrome with protean ectodermal abnormalities in 2003 (Paznekas *et al.*, 2003). With relevance to the skin, 16 different missense mutations (p.Y17S, p.S18P, p.G21R, p.G22E, p.K23T, p.A40V, p.Q49K, p.R76S, p.L90V, p.Y98C, p.K102N, p.I130T, p.K134E, p.G138R, p.R202H, and p.V216L) and a one codon insertion (154_156dupTTT) were delineated in individuals with oculodentodigital dysplasia (OMIM164200) (Paznekas *et al.*, 2003). Oculodentodigital dysplasia is an autosomal-dominant disorder and its typical findings are microphthalmos, small nose, dental anomalies, microcephaly, developmental abnormalities of the hands and feet including syndactyly, brittle nails, and hypotrichosis. Recently, a further case of oculodentodigital dysplasia with an additional clinical feature of palmoplantar keratoderma, resulting from the heterozygous deletion mutation in connexin 43, 780–781del, has been described (Gong et al., 2006), along with a further report of oculodentodigital dysplasia with curly hair and hyperkeratosis caused by a missense mutation, p.L11P, on one allele (Kelly *et al.*, 2006). This study by Gong *et al.* (2006) also showed that the mutant connexin 43 resulted in abnormal gap junction function in keratinocytes, thus expanding the spectrum of connexin genodermatoses.

Adherens junctions

Adherens junctions are electron dense transmembranous structures that associate with the actin cytoskeleton (Vasioukhin and Fuchs, 2001). In their absence, the formation of other cell–cell junctions, such as desmosomes, is compromised. The extracellular domain contains cadherins, such as E-cadherin, which are responsible for homotypic, calcium-dependent, adhesive interactions with cadherins on adjacent cells. Within the cell, cadherins bind to p120ctn, β-catenin, and plakoglobin. p120ctn promotes cell migration through recruiting and activating small GTPases. β-catenin is normally involved in adherens junction formation through its ability to bind to itself and to link cadherins to the actin cytoskeleton However, β-catenin can fulfill another role in acting as a transcriptional cofactor when stimulated by the Wnt signal-transduction pathway. The first naturally occurring mutation in a component of adherens junctions was reported in 2000 in plakoglobin in individuals with Naxos disease (McKoy *et al.*, 2000 discussed in section on desmosomes below) and thus far the only other human adherens junction gene mutation with dermatologic relevance has involved P-cadherin (Sprecher *et al.*, 2001).

P-cadherin

In 2001, a homozygous deletion mutation, c. 981delG, in the *CDH3* gene which encodes the classical cadherin, P-cadherin, was identified in individuals with hypotrichosis with juvenile macular dystrophy (OMIM601553; Sprecher *et al.*, 2001). This autosomal-recessive disorder is characterized by early hair loss followed by progressive degeneration of the central retina, culminating in blindness. P-cadherin is strongly expressed in both the hair follicle and retinal pigment epithelium and the disorder is thought to result from loss of cell–cell adhesion in hair follicle and the retina or defective *wnt*/β-catenin signaling or a combination of both mechanisms. Further homozygous loss-of-function mutations in the *CDH3* gene have been reported, comprising p.L168X, c.462delT, c.829delG, and c.2112delG (Indelman *et al.*, 2003, 2005). In addition, a homozygous missense mutation, p.R503H, which disrupts a critical calcium binding domain within the fourth extracellular domain of P-cadherin, has been identified (Indelman *et al.*, 2002), as well as two different compound heterozygous mutations, IVS2 + 1G > A and p.E504K, and p.R221X, and p.H575R (Indelman *et al.*, 2006). The clinical phenotype of hypotrichosis with juvenile macular dystrophy is fairly consistent: children have short, sparse hair, and progressive loss of vision and blindness develops between the first and third decades. However, the mutation c.829delG, on both alleles of *CDH3*, has recently been reported in a different disorder, ectodermal dysplasia, ectrodactyly, macular dystrophy syndrome (OMIM225280) (Kjaer *et al.*, 2005). In this autosomal-recessive condition there is hypotrichosis, macular degeneration, hypodontia and limb defects, including ectrodactyly, syndactyly, and camptodactyly (Kjaer *et al.*, 2005). A further homozygous missense mutation in P-cadherin, p.N322I, has also been identified in ectodermal dysplasia, ectrodactyly, macular dystrophy syndrome (Kjaer *et al.*, 2005). The reasons for the phenotypic disparity between hypotrichosis with juvenile macular dystrophy and ectodermal dysplasia, ectrodactyly, macular dystrophy syndrome resulting from the same or similar mutations in the *CDH3* gene are not known, although co-inheritance of a mutation in a neighboring gene such as *CDH1* (encoding E-cadherin) has been postulated (Kjaer *et al.*, 2005).

Desmosomes

Desmosomes are important cell–cell adhesion junctions found predominantly in the epidermis and the heart (Green and Gaudry, 2000). Functionally, they consist of three families of proteins, namely the armadillo proteins

(plakoglobin and certain plakophilins (PKPs)), cadherins (three desmocollins and four desmogleins (DSGs)) and plakins (desmoplakin (DSP), envoplakin, periplakin, plectin, bullous pemphigoid antigen 1, corneodesmosin (*CDSN*), and microtubule actin cross-linking factor). Desmosomes provide strength and rigidity to cells and contribute to tissue morphogenesis and certain cellular processes. The first human mutations in a desmosome were identified in the *PKP1* gene, in 1997 (McGrath *et al.*, 1997) and subsequently autosomal-recessive mutations have been identified in DSP, plakoglobin, and DSG4 (Figure 3). Autosomal-dominant mutations have been reported in PKP2, DSP, DSG1 and 2, and CDSN (Figure 3). Collectively, the human mutations demonstrate the important role of several desmosomal proteins in skin, hair, and cardiac development and function.

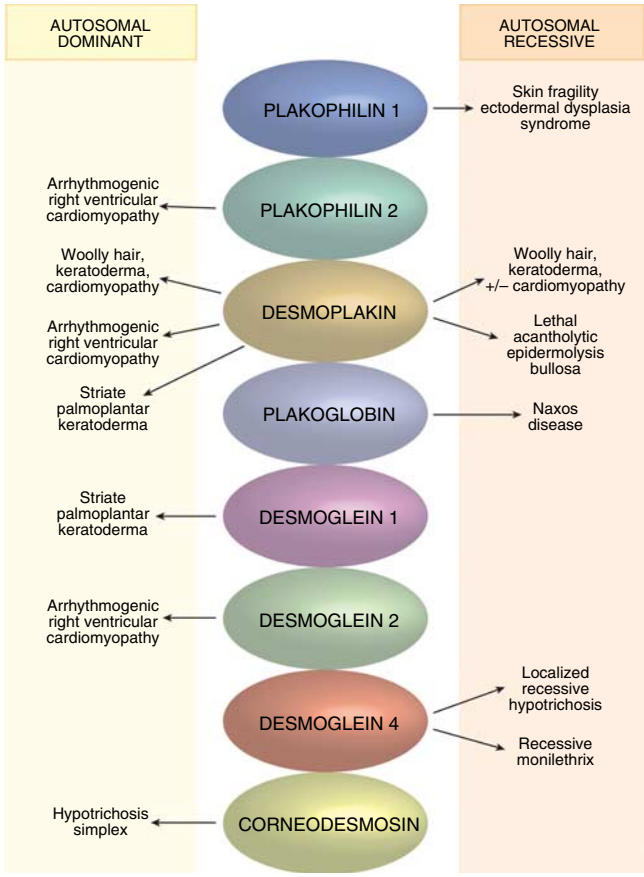

Figure 3. Illustration of the autosomal-dominant and -recessive disease phenotypes associated with inherited mutations in structural components of desmosomes. Mutations in five proteins are associated with dominant diseases: PKP2, DSP, DSG1, DSG2, and CDSN, whereas mutations in four proteins, PKP1, DSP, plakoglobin, and DSG4 have been detected in autosomal-recessive disorders. Only DSP may harbor both dominant and recessive pathogenic mutations.

PKP1

In 1997, McGrath *et al.* (1997) described a child with a combination of skin fragility and inflammation (erosions, fissures, scale-crust, keratoderma) and abnormalities of ectodermal development (small size, scanty hair, reduced sweating, astigmatism) who was a compound heterozygote for loss-of-function mutations on both alleles of the *PKP1* gene, p.Q304X and c.1132ins28; these mutations occur within the second and fourth *arm*-repeats of the protein (Heid *et al.*, 1994; Choi and Weis, 2005) (Figure 4a). Clinically, the unique constellation of signs was termed ectodermal dysplasia-skin fragility syndrome (OMIM604536). Clues to the desmosomal pathology in this case came from skin biopsy analysis, which showed widening of spaces between keratinocytes throughout most of the epidermis (apart from the basal layer) with ultrastructural evidence of a reduced number of small, poorly formed desmosomes. A candidate gene approach (based on reduced/absent expression of desmosomal proteins using immunofluorescence microscopy) was then used to identify the primary abnormalities in PKP1. Subsequently, eight other cases of ectodermal dysplasia-skin fragility syndrome have been reported. In total, nine different *PKP1* mutations have been published, which include one nonsense (p.Y71X), one frameshift (c.888delC) and seven splice site mutations (IVS1−1G>A, IVS4−2A>G, [c.1053T>A+IVS5+1G>T], IVS6−2A>T, IVS9+1G>A, IVS10−2G>T, and IVS11+1G>A (McGrath *et al.*, 1999; Whittock *et al.*, 2000; Hamada *et al.*, 2002; Sprecher *et al.*, 2004; Steijlen *et al.*, 2004; Zheng *et al.*, 2005; Ersoy-Evans *et al.*, 2006). Thus, mutations have been found within the amino terminus as well as the second, third, fourth, seventh, eighth, and ninth arm-repeat domains of PKP1. In six of the nine cases, the mutations have been homozygous. One splice site mutation, IVS1−1G>A, has been reported in two different families (on one allele in a British patient; on both alleles in an Israeli case) (McGrath *et al.*, 1999; Sprecher *et al.*, 2004). From the few mutations reported, limited genotype–phenotype correlation has been possible, although the case reported by Steijlen *et al.* (2004) highlighted a slightly milder clinical variant of the syndrome, perhaps due to presence of at least one in-frame transcript arising from the homozygous splice site mutation, IVS9+1G>A. In addition, the hypohidrosis reported in the original case (McGrath *et al.*, 1997) has not been a persistent feature in clinical follow-up of this patient nor any of the other descriptions of ectodermal dysplasia-skin fragility syndrome. Collectively, the loss-of-function mutations in *PKP1* and cell biologic studies on keratinocytes lacking PKP1, demonstrate the importance of PKP1 in the formation of desmosomal plaques and in stabilizing desmosomal proteins (South *et al.* 2003).

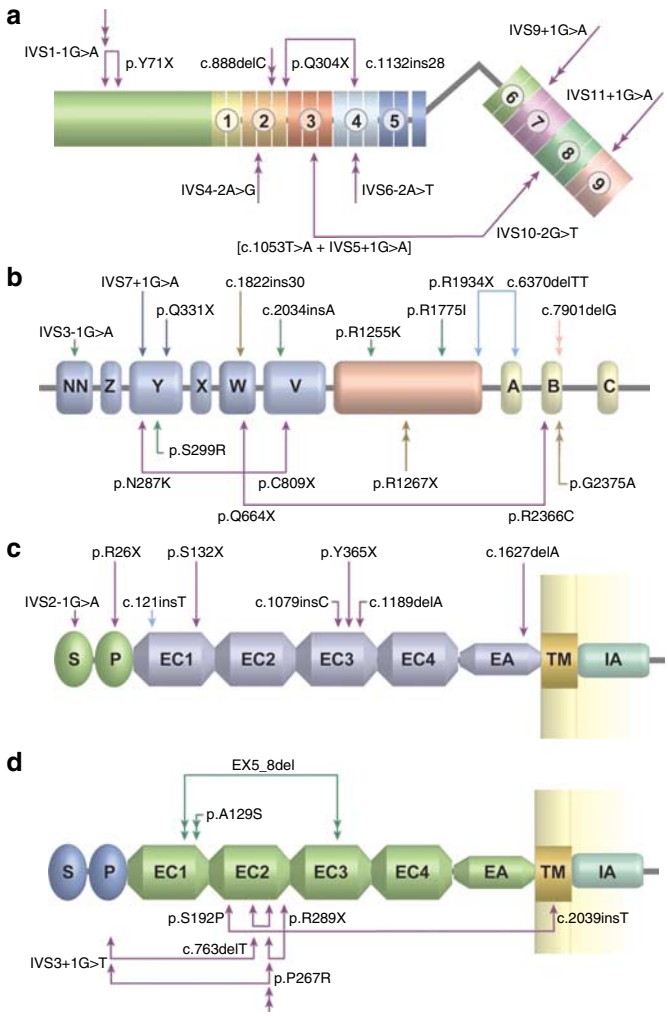

Figure 4. Mutation spectrum and disease phenotypes for the desmosomal proteins PKP1, DSP, DSG 1 and 4. (**a**) Mutations in PKP1: 11 different loss-of-function mutations have been reported all of which are associated with skin fragility-ectodermal dysplasia syndrome. (**b**) Mutations in DSP: 17 different mutations have been reported and lead to various clinical abnormalities comprising striate palmoplantar keratoderma (dark blue arrows); Carvajal syndrome (pink arrows); woolly hair and keratoderma (purple arrows), arrhythmogenic right ventricular cardiomyopathy (green arrows); woolly hair, keratoderma/blisters, cardiomyopathy/Carvajal-like disorder (brown arrows); and lethal acantholytic epidermolysis bullosa (light blue arrows). (**c**) Mutations in DSG1: eight autosomal-dominant mutations have been described, most of which lead to striate palmoplantar keratoderma (purple arrows), although one case of focal keratoderma with additional non-acral hyperkeratosis has been reported (blue arrow). (**d**) Mutations in DSG4: eight different recessive mutations have been identified in either recessive localized hypotrichosis (green arrows) or recessive monilethrix (purple arrows). (Single unconnected arrows represent autosomal-dominant mutations; double arrows indicate homozygous-recessive mutations; joined arrows depict compound heterozygous-recessive mutations).

PKP1 has been shown to bind to DSG1, desmocollin 1, DSP, keratin (at least *in vitro*) and actin (Hatzfeld, 2006), and in the skin of patients with ectodermal dysplasia-skin fragility syndrome, there is altered distribution of DSP, providing direct evidence for the *in vivo* association between PKP1 and DSP (McGrath *et al.* 1997). PKP1 also localizes to nuclei as well as desmosomes, including in several tissues that do not contain desmosomes. The PKP1a isoform can associate with desmosomes or localize to the nucleus whereas PKP1b has an exclusively nuclear localization (Schmidt *et al.*, 1997). However, the role of PKP1 in intranuclear signaling has not been established and how or whether such a role contributes to the ectodermal dysplasia phenotype remains speculative.

PKP2

Heterozygous mutations in the PKP2 gene (*PKP2*) represent the major cause of familial arrhythmogenic ventricular cardiomyopathy (ARVC) (van Tintelen *et al.*, 2006). ARVC is an autosomal-dominant condition characterized by ventricular arrhythmias, syncope, and sudden death usually precipitated by exertion (Thiene *et al.*, 1988). The disorder affects about one in 1250 people and 50–80% of cases are familial (Peters, 2006); non-familial cases do not usually involve *PKP2* mutations (van Tintelen *et al.*, 2006). Expression of ARVC occurs by adolescence and penetrance is approximately 55% (Antoniades *et al.*, 2006). Histologically, the myocardium is replaced by a fibrofatty infiltration and an inflammatory infiltrate, mainly in the right ventricle, apex, inflow, and outflow tracts. The left ventricle can be affected in up to 50% of cases (MacRae *et al.*, 2006). The first *PKP2* mutations in ARVC were reported in 2004 (Gerull *et al.*, 2004): 24 different mutations (nonsense, frameshift, splice site, and missense) were identified in 32 different individuals, with the mutation p.R79X representing a recurrent mutation in several individuals. Several other mutations in familial ARVC have been subsequently identified (Antoniades *et al.*, 2006; Peters, 2006), although no particular cutaneous abnormalities have been reported in any individual with *PKP2* gene pathology. Clinical symptoms associated with ARVC in individuals with heterozygous mutations in *PKP2* are very variable, from no symptoms to tachycardia, syncope, and sudden death, although electrocardiographic abnormalities (e.g. T wave inversion and QRS dispersion) are typically present (Syrris *et al.*, 2006). Involvement of the left ventricle may be an independent risk factor for sudden death (Antoniades *et al.*, 2006).

DSP

The first evidence for a human inherited abnormality of DSP, emerged from a linkage study, that mapped an

autosomal-dominant pedigree with striate palmoplantar keratoderma (SPPK) to 6p24, a locus containing the *DSP* gene (Armstrong *et al.*, 1999) (Figure 4b). Electron microscopy of palmar skin showed dysadhesion between suprabasal keratinocytes with abnormal cell–cell and cell membrane-cytoskeletal adhesion and screening of genomic DNA from affected family members identified a heterozygous nonsense mutation, p.Q331X, in the *DSP* gene (Armstrong *et al.*, 1999). Thus SPPK in this family was due to DSP haploinsufficiency, demonstrating that 50% of normal DSP levels is sufficient for normal epidermal functioning in non-palmoplantar skin but that this amount of DSP is not sufficient to withstand trauma to the palms and soles without resulting in an abnormal phenotype. A second pedigree with SPPK associated with DSP haploinsufficiency was subsequently described, the pathogenic abnormality being a heterozygous donor splice site mutation, IVS7 + 1G > A. (Whittock *et al.*, 1999). The first recessive pathogenic mutation found in the *DSP* gene was a homozygous frameshift mutation, c.7901delG, identified in affected members of three Ecuadorean families (Norgett *et al.*, 2000) with Carvajal syndrome (OMIM605676), which comprises palmoplantar keratoderma, dilated left ventricular cardiomyopathy, and woolly hair (Carvajal-Huerta, 1998). This mutation produces a stop codon leading to the formation of a truncated protein lacking the carboxyl terminal tail domain. In this syndrome, affected patients suffer from heart failure in their teens and the skin abnormalities are usually confined to areas prone to mechanical stress such as the palms and soles. Contrastingly, the almost complete ablation of the DSP tail may produce an even more severe phenotype consisting of progressive widespread epidermolysis associated with generalized alopecia, absence of nails, and the presence of neonatal teeth (Jonkman *et al.*, 2005). This condition, termed ''lethal acantholytic epidermolysis bullosa'' (OMIM609638) has been described in a single neonate who was a compound heterozygote for two novel mutations in the *DSP* gene, p.R1934X, and c.6370delTT. Further homozygous missense (p.G2375R) and nonsense (p.R1267X) mutations in the *DSP* gene have also been reported (Alcalai *et al.*, 2003; Uzumcu *et al.*, 2006): the phenotype in affected individuals involves abnormalities in the skin (blisters or palmoplantar keratoderma), hair (woolly), and heart (arrhythmogenic right ventricular cardiomyopathy). The mutation p.R1267X specifically truncates the DSPI isoform of DSP: alternative splicing of DSP creates two DSP transcripts, a larger DSPI and a smaller DSPII, with both isoforms contributing to the organization of the cadherin–plakoglobin complex (Smith and Fuchs, 1998; Kowalczyk *et al.*, 1999), but only DSPI is found in cardiac tissue (Angst *et al.*, 1990). Another recessive DSP phenotype, consisting of keratoderma, woolly hair, and nail dystrophy but without cardiac abnormalities, has been described and termed ''skin fragility-woolly hair syndrome'' (OMIM607655) (Whittock *et al.*, 2002). Two unrelated cases were found to be compound heterozygotes for different combinations of nonsense/missense mutations in *DSP*, p.C809X/p.N287K, and p.Q664X/p.R2366C. Heterozygous carriers of the respective nonsense mutations in these families, however, had no phenotypic abnormalities, an unexpected observation given the two earlier reports of DSP haploinsufficiency in SPPK (Armstrong *et al.* 1999; Whittock *et al.*, 1999). Heterozygous carriers of the respective missense mutations also have no phenotypic abnormalities, although a number of other autosomal-dominant missense mutations (p.S299R, p.R1255K, and p.R1775I) have been reported in pedigrees with ARVC (right or left ventricular involvement) (Rampazzo *et al.*, 2002; Bauce *et al.*, 2005) and similar disorders have been described for the heterozygous mutations IVS3−1G > A (Bauce *et al.*, 2005) and c.2034insA (Norman *et al.*, 2005). One further heterozygous mutation in the *DSP* gene has been reported, an insertion of 10 amino-acid residues, starting in codon 608, designated c.1822ins30 (Norgett *et al.*, 2006), in which the clinical features comprised ARVC, woolly hair and PPK. Thus far, 17 different mutations have been reported in the *DSP* gene. These comprise five nonsense, six missense, four frameshift, and two splice site mutations. Clinically, mutations in *DSP* result in a variable combination of skin, hair, and cardiac abnormalities. The pattern of the keratoderma is not always ''striate'': sometimes it appears more focal, sometimes more diffuse. Moreover, the age of onset is variable and the degree of trauma to the palms and soles clearly has an influence on the clinical severity and presentation. The subtype of cardiomyopathy is also variable, with different degrees of right ventricular (as in most reports) or left ventricular involvement. Nevertheless, often both ventricles show dysfunctional abnormalities and premature cardiac death (from arrhythmia) is common to nearly all cases with myocardial involvement.

Plakoglobin

Only one pathogenic mutation in the human plakoglobin gene (*JUP*) has been reported (McKoy *et al.*, 2000). A homozygous 2-base pair deletion, c.2157delTG, was shown to be the cause of an autosomal-recessive disorder involving heart, skin, and hair abnormalities known as Naxos disease (OMIM601214), following an earlier report that mapped this condition to 17q21 (Coonar *et al.*, 1998). Moreover, plakoglobin-deficient transgenic mice had been shown to have severe cardiac defects and, in those that survived, skin fragility was observed (Bierkamp *et al.*, 1996) and thus the *JUP* gene represented an attractive candidate for a human cardiocutaneous syndrome. The clinical features of Naxos disease comprise ARVC, nonepidermolytic diffuse PPK, and irregular woolly hair. The disorder is named after the Mediterranean island Naxos on which approximately 1 in 1,000 of the population are affected (Antoniades *et al.*, 2006), although additional cases have been documented on the neighboring island of Milos and in Bologna (Italy). In total, approximately 30 cases have been reported and all have the same mutation. The mutation c.2157delTG occurs close to the carboxyl terminus of plakoglobin and alters the last five amino acids within the 13th

arm-repeat, truncating the protein by 56 residues. The dermatologic features of PPK and woolly hair are present in all individuals who are homozygous for the c.2157delTG mutation with no reports of skin or hair abnormalities in heterozygous carriers. In homozygous individuals, over 90% have electrocardiographic abnormalities compared to about 25% of heterozygous carriers (who have mostly T wave inversion in the V1–V3 leads). Cardiac features in homozygous subjects include arrhythmias, syncope, heart failure, and sudden death but heterozygotes show no overall increased cardiac morbidity or mortality (Antoniades *et al*., 2006).

DSG1

Abnormalities in the *DSG*1 gene in an inherited skin disorder were first identified in 1999. Rickman *et al*. (1999) mapped a three-generation Dutch family with SPPK to 18q12.1 and identified a heterozygous acceptor splice site mutation, IVS2−1G>A, in the *DSG1* gene (Figure 4c). This mutation occurs within the prosequence of *DSG*1 but results in skipping of exons 2–4 and generating a peptide that is only 25 amino acids in length. This finding suggests that the SPPK in this family (OMIM148700) is due to haploinsufficiency of DSG1. Six further mutations in *DSG1*, p.R26X, p.S132X c.1079insC, p.Y365X, c.1189delA, and c.1627delA were then reported (Hunt *et al*., 2001; Kljuic *et al*., 2003b). All of these mutations are located within the extracellular part of DSG1. Clinically, affected individuals had features of SPPK, but none had any abnormalities in nonpalmoplantar skin or skin appendages, including hair. Although dominant-negative interference between the wild-type and mutant alleles could not be completely discounted, the disease pathophysiology in all these cases was presumed to be due to DSG1 haploinsufficiency. Subsequently, the mutation p.R26X was also reported in an Israeli pedigree with autosomal-dominant keratoderma (Keren *et al*., 2005). However, the pattern of skin thickening on the palms in this family was not striate. Rather, affected individuals had diffuse nonepidermolytic PPK although there was no involvement of other skin sites. In contrast, Milingou *et al*. (2006) described an individual with DSG1 haploinsufficiency, owing to a heterozygous frameshift mutation, c.121insT, who had clinical features of focal (rather than striate) PPK as well as skin thickening/scaling on trauma-prone sites such as the knees, ankles, or finger knuckles; the patient also had mild nail dystrophy. Clearly, in all cases of *DSG1* mutations, trauma has a significant impact on disease expression and severity. Mutations in the *DSG1* gene also affect the number and size of desmosomes as well as expression of other skin proteins (Wan *et al*., 2004). Notably, in palmar skin, DSG1 haploinsufficiency leads to a reduced number of smaller desmosomes in suprabasal layers. By confocal microscopy, there is reduced expression of keratins K5, K14, and K10 and upregulation of K16; involucrin labeling is also disrupted (Wan *et al*., 2004).

DSG2

The first pathogenic mutations in the human gene (*DSG2*) were identified in 2006 (Awad *et al*., 2006; Pilichou *et al*., 2006). Given the predominant localization of DSG2 in cardiac myocytes and the earlier descriptions of mutations in the desmosomal proteins DSP, JUP, and PKP2 in individuals and families with ARVC, the *DSG2* gene represented a plausible candidate for mutations in unclassified cases. Fourteen mutations were identified: p.R45Q, p.R48H, p.Y87C, p.G100R, p.N266S, p.K294E, p.W305X, p.E331K, c.1253insATGA, IVS12−2A>G, p.C506Y, c.2036delG, p.Q558X, and p.G811C (Awad *et al*., 2006; Pilichou *et al*., 2006). Most of these were dominantly inherited. However, the mutation p.E331K occurred on the same allele as the splice site mutation IVS12−2A>G and may therefore represent a rare missense polymorphism. In addition, two of the mutations occurred in one individual who was a compound heterozygote for p.R48H and p.W304X. This individual also had a history of an episode of erythema multiforme/Stevens–Johnson syndrome associated with extensive mucosal ulceration, as well as a separate episode of a severe postoperative wound infection (Awad *et al*., 2006). However, none of the other individuals in either report had any recorded skin, hair, or mucosal abnormalities. Most of the pathogenic mutations identified are located within the extracellular adhesive domain of DSG2. The clinicopathological features of ARVC in individuals with *DSG2* mutations are similar to those cases with mutations in other desmosomal components, with left ventricular involvement in up to 50% of affected subjects. Overall, it appears that *DSG2* mutations account for about 5–10% of all cases of ARVC and that, collectively, mutations in structural components of the desmosomal complex provide the genetic basis for approximately 40% of ARVC.

DSG4

The first inherited disorder owing to mutations in the *DSG*4 gene was identified in 2003 (Kljuic *et al*., 2003a). A homozygous intragenic deletion was shown to be the cause of localized autosomal-recessive hypotrichosis (OMIM607903) (Figure 4d), although this disorder appears to be genetically heterogeneous with other cases mapping to chromosome 3q (Aslam *et al*., 2004). Clinically, affected individuals have hypotrichosis involving the scalp, chest, arms, and legs, but there is sparing of the axillary and pubic hair and eyelashes. On the scalp, small papules are present owing to the inability of the hair to extrude through the skin (Kljuic *et al*., 2003a). The deletion mutation first identified, EX5–8del, has been shown to be a recurrent mutation in several Pakistani families (Moss *et al*., 2004; Rafiq *et al*., 2004; John *et al*., 2006; Kljuic *et al*., 2003a). This mutation deletes all of the second extracellular domain as well as part of the first and third extracellular domains. A homozygous missense mutation, p.A129S, has also been reported in an Iraqi subject with localized autosomal-recessive hypotrichosis (Messenger *et al*., 2005). This amino-acid substitution is located within a highly conserved motif (RAL) corresponding to the HAV region of classical cadherins, a domain that is important in cell adhesion. In 2006, further missense (p.P267Rp.S192P), splice site (IVS3+1G>T), frameshift

(c763delT; c.2039insT), and nonsense (p.R298X) mutations in the *DSG4* gene were reported (Schaffer *et al.*, 2006; Shimomura *et al.*, 2006; Zlotogorski *et al.*, 2006). However, the phenotype in these cases was described as autosomal-recessive monilethrix. Although the beaded hair phenotype of monilethrix typically presents as an autosomal-dominant disorder (OMIM158000) owing to heterozygous mutations in the hair keratin genes, *KRTHB1*, *KRTHB3*, and *KRTHB6*, recessive forms of the disease also exist and these appear to result from mutations on both alleles of *DSG4*. The six different autosomal-recessive mutations that have been reported were described in individuals from Iran, Iraq, Morocco, and Japan (Schaffer *et al.*, 2006; Shimomura *et al.*, 2006; Zlotogorski *et al.*, 2006). One of these mutations, p.P267R, appears to be a recurrent mutation in the Jewish Iraqi population (Schaffer *et al.*, 2006; Zlotogorski *et al.*, 2006). Five of the mutations are located within the extracellular part of DSG4, either in the pre-protein domain or in the first two extracellular domains, and one mutation (c.2039insT) occurs within the transmembranous region. Although localized autosomal-recessive hypotrichosis and recessive monilethrix are listed as distinct entities, some phenotypic overlap exists and the nature of the mutations in the extracellular part of DSG4 also shows similar gene pathologies.

CDSN

Within cornifying squamous epithelia, one additional desmosomal component is CDSN, a glycoprotein that is also expressed in the inner toot sheath of the hair follicle. In 2003, heterozygous nonsense mutations in the *CDSN* gene, were identified in individuals with the autosomal-dominant disorder hypotrichosis simplex (OMIM146520) (Levy-Nissenbaum *et al.*, 2003). In this condition, hair is usually normal at birth but progressive thinning of scalp hair starts within the first decade and is almost complete by the third decade; other body sites are not affected. Affected individuals within an Israeli and a Spanish family were heterozygous for the mutation p.Q215X, whereas the *CDSN* gene pathology in a Danish family involved the heterozygous nonsense mutation p.Q200X. A third nonsense mutation, p.Y239X, has also been reported in a Mexican pedigree with hypotrichosis simplex (Dávalos *et al.*, 2005) Histologically, there is a loss of cohesion in the inner root sheaths. Moreover, proteolytically cleaved aggregates of abnormal CDSN accumulate around hair follicles and in the superficial dermis and it has been suggested that these aggregates are toxic to the hair follicle cells and that hypotrichosis simplex of the scalp is a disease associated with protein misfolding (Levy-Nissenbaum *et al.*, 2003).

Conclusion

The identification of a large number of naturally occurring human mutations in genes encoding proteins that contribute to intercellular junctions has provided a fascinating insight into the etiology of a spectrum of inherited diseases, many with rare and unusual phenotypes. Delineating particular mutations has also led to valuable new data on the functional role of specific domains of certain proteins in both health and disease states, as well as providing new ideas and opportunities for both basic and translational research.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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